Synopsis on the proposed area of research related to Ph.D work

Theoretical Investigation on the mechanistic pathways of transition metal catalyzed Cyclisation Reactions.

Submitted By

Rohini Saha

Enrolment Id:03333331701
Registration No. :- VB-256 of 2008-09

Under supervision of
Dr. Gourab Kanti Das

Department of Chemistry
Siksha-Bhvana(Institute of Science)
Visva-Bharati
Santiniketan-731235
West Bengal

Synopsis of proposed Ph.D work

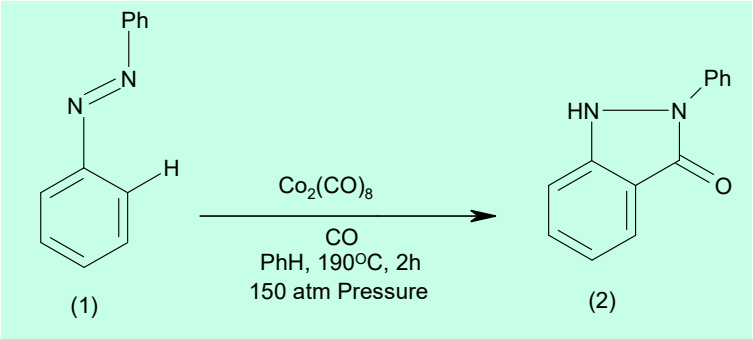
Title of the project: Theoretical Investigation on the mechanistic pathways of transition metal catalyzed Cyclisation Reactions.

A brief overview about the project & a short literature review:

Past few decades have witnessed the rapid development of the trantision metal catalyzed organic transformations that serve as the useful tools for the synthesis of several natural products. Initially the second and third row metals like Pd, Rh were used as catalyst for functionalization in organic molecules. Palladium metal salts were involved in Heck, Suzuki, Sonogashira, types of coupling reactions. The Wilkinson's catalyst containing Rh was used for hydrogen addition to substrate. After a long period of time it was found that the coinage metals like Au, Ag, Cu and heavy metal like Pt, Ir, Ru etc catalyse several useful transformation in organic chemistry.

In recent years considerable attention have been given in the transition-metal catalyzed C-H functionalization. Until recently, the majority of catalyzed C-H functionalization was made using very costly second and third row transition metals. The usage of catalysis based on the cost-effective 3d transition metal complexes represents an attractive alternative. As a result the use of inexpensive first-row transition metal catalysis for C-H functionalization has gained considerable attention. Among them the cobalt complexes, those are environmentally benign, have great potential for applications in homogeneous catalysis. The most notable starting point in the effective use of cobalt complexes was found in 1941, by Karash and Fields[1], which shows homocoupling of Grignard reagents. Subsequently, research on these metal complexes has turned cobalt into one of the most effective metal for future use in homogeneous catalysis. Some of the applications include hydroformylations[2] and the Phausen-khand reaction. Many studies have recently been undertaken to utilize easily available cobalt complexes for C-H activation chemistry.

On isolation and characterization of cyclometalated cobalt complex, Klein[3] and co-workers show the elementary step of C-H cobaltation. Murahashi[4,5] reported a cobalt-catalyzed carbonylative cyclisation of azobenzene (1) to indazole (2) that represent early examples of chelation-assisted C-H functionalization reactions. (Scheme-1)



Scheme-1

Though the above process pointed out the potentially in cobalt complexes for C-H actvation and functionalization, further applications were largely limited by the rather drastic reaction conditions, that is a reaction temperature of 190°C at a high pressure. The development of modern cobalt catalysed C-H functionalization remained dormant, until Kisch[6] and co-workers reported the first cobalt catalysed hydroarylation of alkynes using a cobalt(I) complex. Based on this work, the development of hydroarylation of alkynes and olefins by cobalt salt gained a significant speed during the last five years. Yoshikai and co-workers devised a ternary catalytic system consisting of $CoBr_2$, a phosphine ligand and a Grignard reagent as stoichiometric reductant to catalyze the hydroarylation of alkynes. Imines also turned out to be powerful directing groups.[7] Additions of aryl ketimines or aldemines to internal alkynes were achieved by a $CoBr_2$, a phosphine ligand, a Grignard reagent and pyridine.[8]

Brookhart's[9,10] studies on Cp*Co(I) complexes for hydroacylation indicates the unique potential of the Cp* ligand motif for cobalt catalysed C-H functionalization. The direct addition of 2-arylpyridines to imines, and α,β-unsaturated enones using the Cp*Cobalt(III) complexe was described by Matsunaga/Kanai.[11,12]

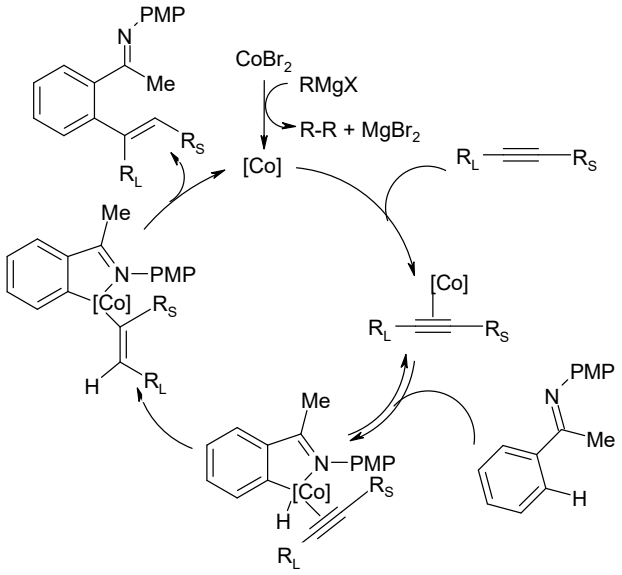
While proposing the mechanism of the cobalt catalysed activation of C-H bond followed by the functionalization, two types of pathway have been proposed.

In the first case, where the transformation are carried out by the utilisation of Grignard reagent to produce an ill-defined low valent cobalt complex,[8,13,14] the oxidative addition of the ortho C-H bond clearly suggests a formation of intermediate where Co is bonded to a hydrogen atom (scheme-2a). Intramolecular hydrocobaltation of the complex intermediate and subsequent reductive elimination of the next intermediate furnish the desired product and regenerate the cobalt catalyst.

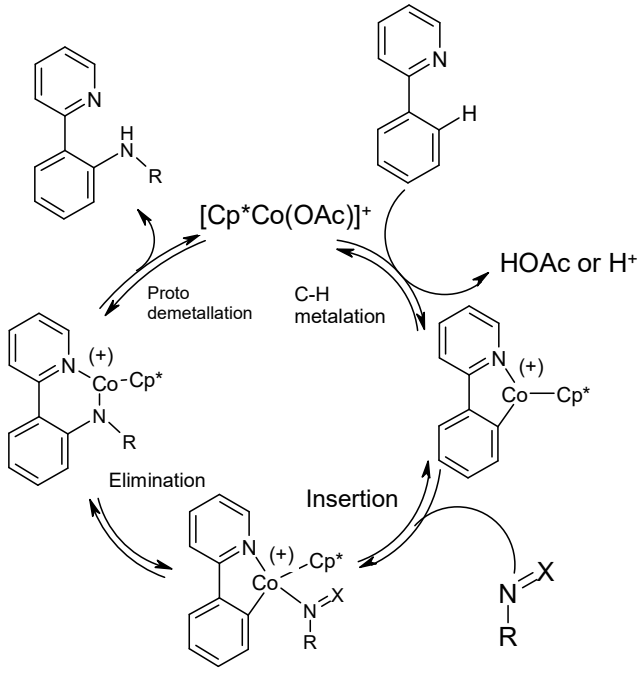
However the mechanism the Cp* ligand when present to stabilise the cobalt complex suggests a different pathway. The proposed catalytic cycle shows a carboxylate assisted hydroarylation/ annulations sequence that is supported by the experiments with isotopically labelled substrates. The selective H/D scrambling at the C-2 position, which provided strong evidence for the carboxylate assisted C-H actvation to be operative, put forward such a concerted metalation deprotonation (CMD) pathway.[15,16] In this case (scheme-2b) the mechanism starts by the dissociation of the benzene ligand as well as ligand exchange with acetate ion. The neutral complex $[Cp^*Co(OAc)_2]$ on further dissociation delivers the catalytically active cationic complex $[Cp^*Co(OAc)]^+$. The complex on coordination with substrate undergoes an acetate-assisted[17] C-H activation to deliver the cyclometalated complex. This is followed by insertion and proto-demetalation step to produce the final product.

The above discussion cleary reveals that the mechanistic pathway in C-H metalation by Co-catalyst depends on the nature of the ligands present on the metal ion. In absence of Cp* ligand, the oxidative addition leads to an intermediate where the metal is attached to a hydrogen atom. Presence of Cp* ligand after such pathway and promotes a ligand assisted conserted metalation deprotonation(CMD) pathway for activating the aromatic ring. Other experimental observation also reveals that the presence of phosphene or NHC(N-heterocyclic carbene) as ligand plays critical role

in directing the reaction to the product. These features promote us to study the effect of the ligand on the cobalt catalyzed C-H metalation and serve as a part of study in the present proposal.



(a)



(b)

Scheme-2

In addition to the above plan our next attention is on the reaction mechanism of organic transformation of the Pt-metal catalyzed reactions. Platinum metal complexes that have been exploited in many reactions specially activate the unsaturated compounds. As there is much similarity between the reactivity of double bond and cyclopropane ring system it is not surprising that the metal atom can activate this small membered ring in many ways. Zeise's salt, the first organometallic compound isolated in the year of 1827, is one of the platinum metal complexes isolated in monomeric and dimeric forms. Though the catalytic activity of many platinum complexes on a variety of substrates has been reported in past one or two decades, the action of Zeise's salt is surprisingly found to be limited to certain substrates. Out of these few reports the most promising cases are the reaction with cyclopropane derivative. While proposing the mechanistic pathway the researchers use to suggest the initial activation of the cyclopropane moiety by forming a coordinate bond to the metal centre. On progress through the reaction pathway the metal atom on oxidative addition gets inserted into the cyclopropane ring forming a platina-cyclobutane derivate. Recent report on the study of ^{13}C-NMR data shows the formation of this metal cyclobutane derivate as an effective intermediate in the reaction pathway. This intermediate, on subsequent rearrangement transforms to the final product of cyclopentane derivative. Though the proposed pathway gives us a qualitative picture of mechanism of the reaction it cannot explain several side reactions associated with the main ring breaking process. Our preliminary study on one such reaction reveals that the formation of the initial complex requires two platinum atoms provided by the Zeise's dimer and many of the side reaction can be explained but assuming the involvement of dimeric form of the Zeise's dimer. To explore in detail the other reactions catalyzed by Zeise's salt we make this plan to study the reaction pathway in full detail by DFT method.

Literature survey reveals that the propargylic ester derivatives undergo several useful transformations under the catalytic action of platinum-salt. In this context we appreciate to mention that we have already gained some experience in the study of the reaction mechanism catalysed by Pt and Au-metal salt. [Arpita Chatterjee, Rohini Saha, Dibyajyoti Panja, Sujit Ghosh, Sonjoy Mondal, Animesh Ghosh, Gourab Kanti Das*. Revisited the mechanism of the transition metal catalyzed cycloetherification of ω-hydroxy propargylic ester: A DFT study, *Computational and Theoretical Chemistry*, 1114 (2017) 146–152]

Objectives:

(a) To collect all the plausible mechanisms of action of homogeneous Co-salt and Pt-salt.
(b) To identify the stationary points involved in the pathway of the plausible mechanisms.
(c) To compare the local and global activation energy involved in each mechanisms. From this data rate determining step of the mechanism will be determined.
(d) To identify the most favorable pathway of the reaction.
(e) To study the effect of substrate variation on the reaction.
(f) To predict the outcomes of other unknown reactions.

Methodology:

For the computational modelling of the proposed project work Quantum Mechanical (QM) methods will be adopted. The most important task of this modelling will be the exploration of the potential energy surface (PES) of the molecular assembly involved in the metal catalysed reactions. The PES is the most complete description of all the conformers, isomers and energetically accessible motions of a molecular system. Our special interest is to locate the stationary points on the PES. Most informative stationary points are the minima and the saddle points. Minima on the potential energy surface (PES) correspond to the optimized geometries. The lowest energy minimum is called the global minimum. The transition structure between the reactions and the products of a reaction is a saddle point on the surface. All the species, like reactant, product and transition state linking these two, are called stationary points. At the stationary point the surface is parallel to the horizontal line corresponding to more than two geometric parameters. Hence, the first derivative of the potential energy with respect to each geometric parameter is zero i.e. $^{dE}/_{dq} = 0$. However, a minimum is a minimum in all directions, but a saddle point is a maximum along the reaction coordinate and a minimum in all other directions. They can be distinguished by the second derivative of energy with respect to the nuclear coordinates. Mathematically it can be written as, at the minimum, $^{d^2E}/_{dq^2} > 0$ for all values of q, at the saddle point, $^{d^2E}/_{dq^2} > 0$ for all q except, along the reaction coordinate. Along the reaction coordinate, $^{d^2E}/_{dq^2} < 0$, a PES can be used to find both the saddle points and the reaction coordinates. To study the real time dynamics of the substrate-cofactor-enzyme assembly the GROMACS software will be used. The plot of Root Mean Square Deviation (RMSD) of the macromolecular structure with time is of immense importance as it demonstrates the conformational changes which are taking place during the entire simulation time. Calculation of the electrostatic potential surface (EPS) of the molecular assembly under investigation will also be studied to explore the electrostatic effect operating in the transition structure of the corresponding reaction.

Year wise plan of work and targets to be achieved:

The first year of the project will be used to explore various Co-catalysed C-metalation and reductive elimination reactions that utilise the Grignard reagent to produce low valent Co-complex as intermediate. Various computational data will also be collected during this period.

The next one year period will be used to study the Co-catalysed concerted metalation deprotonation pathway (CMD) along with other reactions. We will study all these reactions in detail in both gas phase and in solution phase. The potential energy surface will also be explored to find out the mechanistic details and various electrostatic interactions occurring in the transition state.

The last year of the period will be utilised through studying comparative catalytic action of other metals like Au, Pd, Pt etc metals along with the study of Co-catalysed reactions.

References:

1. Kharasch,M.S.; Fields,E.K. *J.Am.Chem.Soc.*1941,63,2316-2320.

2. Hebrard,F.; Kalck,P. *Chem..Rev.* 2009,109,4272-4282.

3. Klein,H.F.; Helwig,M.; Koch,U.; Florke,U.; Haupt,H.J.Z. Natureforsch,B. *J.Chem.Sci.* 1993,48,778-784.

4. Murahashi,S.; Horiie,S. *J.Am.Chem.Soc.* 1956,78,4816-4817.

5. Murahashi,S. *J.Am.Chem.Soc.* 1955,77,6403-6404.

6. Halbritter,G.; Knoch,F.; Wolski,A.; Kisch,H. *Angew.Chem.,Int.Ed.Engl.* 1994,33,1603-1605.

7. Ackermann,L.; Lygin,A.V. *Org.lett.* 2012,14,764-767.

8. (a) Lee,P.S.; Fujita,T.; Yoshikai,N. *J.Am.Chem.Soc.* 2011,133,17288-17295. (b) Tan,B.-H.; Dong,J.; Yoshikai,N. *Angew.Chem.,Int.Ed.* 2012,51,9610-9614. (c) Tan,B.-H.; Yoshikai,N. *Org.Lett.* 2014,16,3392-3395.

9. (a) Lenges,C.P.; Brookhart,M. J.Am.Chem.Soc. 1997,119,3165-3166. (b) Lenges,C.P.; Brookhart,M.; Gant,B.E. *J.Organoment.chem.* 1997,528,199-203.

10. Lenges,C.P.; White,P.S.; Brookhart,M. *J.Am.Chem.Soc.* 1998,120,6965-6979.

11. (a) Nakao,Y.; Yamada,Y.; Kashihara,N.; Hiyama,T. *J.Am.Chem.Soc*. 2010,132,13666-13668. (b) Tsai,C.-C.; Shih,W.-C.; Fang,C.-Y.; Li,C.-Y.; Ong,T.-G.; Yap,G.A.P. *J.Am.Chem.Soc.* 2010,132,111887-11889.

12. Andou,T.; Saga,Y.; Komai,H.; Matsunaga,S.; Kanai,M. *Angew.Chem.Int.Ed* 2013,52,3213-3216.13. Fallon,B.J.; DErat,F.; Amatore,M.; Aubert,C.; Chemla,F.; Ferreira,F.; Perez-Luna,A.; Petit,M. *J.Am.Chem.Soc*. 2015,137,2448-2451.

13. Gao,K.; Yoshikai,N. *Acc.Chem.Res.* 2014,47,1208-1219.

14. Ackermann,L. *Chem.Rev.* 2011,111,1315-1345.

15. Lapointe,D.; Fagnou,K. *Chem.Lett.* 2011,39,1118-1126.

16. Ikemoto,H.; Yoshino,T.; Sakata,K.; Matsunaga,S.; Kanai,M. *J.Am.Chem.Soc*. 2014,136, 5424-5431.

17. Zheng, H., Zheng. J., Yu, B., Chen, Q., Wang, Z., He, Y., Yang, Z., She, X., *J. Am. Chem. Soc.*, 2010, 132, 1788.

18.(a) Zeise, W. C. *Pogg. Am. Phys.* 1827, 9, 632. (b) Zeise, W. C. Magn. Pharm. 1830, 35, 105.

19.(a) Jennings, P. W., Johnson, L. L. Chem. Rev. 1994, 94, 2241. (b) Hoberg, J. O., Jennings, P. W., *Organometallics*, 1996, 15, 3902. (c) Ikura, K., Ryu, I., Kambe, N., Sonoda, N., *J. Am. Chem. Soc.* 1992, 114, 1520. (d) Doyle, M. P., van Leusen, D. *J. Org. Chem.* 1982, 47, 5326. (e) Beyer, J., Skaanderup, P. R., Madsen, R.. *J. Am. Chem. Soc.*, 2000, 122, 9575.